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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Food and Drug Administratio
Waterview Corporate Center
10 Waterview Blvd., 3rd Floo
Parsippany, NJ 07054

Telephone (973) 526-6005

December 29, 2003

WARNING LETTER

CERTIFIED MAIL-
RETURN RECEIPT REQUESTED

Mr. Adrian Adams
President and CEO
Kos Pharmaceutjcals Inc.
1001 Brickell Bay Drive 25th Floor
Miami, Florida 33131

File # 04-NWJ-06

Dear Mr. Adams:

During a July 14 through August 8, 2003, inspection of your firm's prescription drug manufacturing facility located at 18 Mayfield Avenue, Campus 9, Edison, New Jersey, an Investigator from this office documented serious deviations from current Good Manufacturing Practice (cGMP) regulations as delineated in Title 21, Code of Federal Regulations, Parts 210 and 211.

The inspection revealed your firm's Quality and Laboratory systems employed during the manufacture, processing, packing, or holding of Niaspan (niacin extended-release tablets) and Advicor (niacin extended-release tablet cores/lovastatin tablets) do not conform to cGMP. Therefore, these lipid-altering products are adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). The following are examples of the significant deficiencies regarding your firm's Quality and Laboratory systems. These deficiencies were included on the Form FDA-483, List of Inspectional Observations, presented to you on August 8, 2003.

1. **Failure of your Quality Control Unit (QCU) to thoroughly investigate a rejected batch and to evaluate other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy [21 CFR 211.22 and 21 CFR 211.192].**

This issue was previously brought to your attention during an April 2002, inspection at this same facility. Your firm's written response to this office, dated May 9, 2002, stated that "Kos recognizes and agrees that a stronger investigation procedure is needed..." and regarding your corrective action plan at that time, "We believe that the above noted corrective actions will preclude any future failings of the investigation procedure."

As observed during the recent inspection of this facility, not all of your firm's past corrective actions regarding failure investigations have been adequate. For example, your firm's QCU failed to thoroughly investigate dissolution failures in multiple lots of your Niaspan Extended Release tablets and content uniformity failures found in multiple lots of Advicor tablets.

Your QCU attributed the Niaspan dissolution failures seen in [redacted] of [redacted] lots of finished product to a low Hydroxypropyl content ([redacted]) in the Methocel E10M raw material (lot #0205100002) used in the manufacture of the lots. Additionally, [redacted] of [redacted] Niaspan lots produced using Methocel E10M lot #0207200002 also failed dissolution and these failures were also attributed to a low Hydroxypropyl content ([redacted]) in the Methocel raw material. The Hydroxypropyl contents in both circumstances were within your NDA listed specification of [redacted] to [redacted]. This is of particular concern since the Methocel raw material helps to control the rate of release of the drug in your Niaspan product. It is also unclear if your QCU has assessed all of the manufacturing variables needed to optimize your production process in that your Process Evaluation Summary dated February 10, 2003, also identified an increase in the operating temperature as a contributing factor to the dissolution failures.

Your QCU also failed to extend the investigation into other similar lots. The investigation did not include [redacted] marketed lots of Niaspan that were manufactured with the same Methocel used in the rejected lots. Furthermore, [redacted] lots of Niaspan manufactured using a third lot of Methocel E10M, lot #0205100001, also having a Hydroxypropyl content of [redacted], passed dissolution and were released to the market.

Regarding your Advicor product, your QCU failed to properly investigate Content Uniformity failures found in [redacted] lots of Advicor tablets. Specifically, [redacted] lots of Advicor 500mg/20mg and [redacted] lots of Advicor 750mg/20mg failed Content Uniformity release testing and were rejected. Your QCU attributed the failures to low "dew points" of [redacted] respectively. However, your "dew point" specification is no more than [redacted]. The investigation into these failures did not evaluate lots released to the market that had been produced under similar conditions with similar dew points.

Your recent written response, dated September 6, 2003, again promises that failure investigations will be fully conducted and documented and that "Quality Assurance is now undertaking the responsibility for conduct and documentation of failure investigations." Please provide clarification on how this commitment is different than the one in your May 9, 2002 written response.

2. Failure to follow established Standard Operating Procedures regarding the handling of written and oral drug product quality complaints [21 CFR 211.198(a)]

Your firm's QCU failed to follow established written Standard Operating Procedures (SOP) for investigating drug product quality complaints received by your firm. Specifically, your firm's SOP states that it is the responsibility of the support departments (e.g., Quality Assurance, Quality Control, etc.) to complete their part of the complaint investigation "usually within 30 days." Yet, our Investigator observed incomplete complaint investigations lasting as long as 247 and 301 days after receipt of the complaint.

3. Failure to follow written procedures for Annual Product Reviews [21 CFR 211.180(e)(1)].

Your firm's QCU failed to follow established written procedures for conducting Annual Product Reviews (APR). Specifically, the APR for your Niaspan product was approximately 13 months overdue even though your Standard Operating Procedure (SOP #QA-405-00, Drug Product Annual Review) states that the review will be performed at least annually.

4. **Failure to follow established laboratory control procedures [21 CFR 211.160(b)(1)].**

Your firm's laboratory failed to properly label sample preparations in your laboratory refrigerator and workbench areas. Specifically, several sample preparations were observed by our Investigator to be missing a label stating the identity, date of sample preparation and expiry of sample, even though your firm's laboratory SOP requires this information be on each sample preparation in the laboratory.

We received your firm's September 6, 2003, written response which addressed the Form FDA 483 Inspectional Observations issued at the conclusion of the inspection. We will review the implementation and the adequacy of your cGMP corrective actions during our next inspection of your firm. The inspectional findings and your written response were also sent to FDA's Review Division for lipid-lowering drugs. Any questions or concerns they may have will be conveyed under separate correspondence.

The above items are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure that the drug products you manufacture are in compliance with the Act and the regulations promulgated under it. Federal agencies are routinely advised of Warning Letters issued so that they may take this information into account when considering the award of government contracts.

You should take prompt action to correct deficiencies at your facility. Failure to implement corrective measures may result in further regulatory action without notice. These actions may include seizure of your products or injunction.

You should notify this office in writing within 15 working days of receipt of this letter of your corrective action plan to address the deficiencies at your firm. If corrective actions cannot be completed within 15 working days, please state the reason for the delay and the timeframe within which corrective actions will be completed. Your reply should be addressed to the New Jersey District Office, Food and Drug Administration, 10 Waterview Blvd., Parsippany, New Jersey 07054, Attn: Joseph F. McGinnis R.Ph, Compliance Officer.

Sincerely,

Douglas I. Ellsworth
District Director
New Jersey District